**Remarks**

Claims 1-8 and newly-added claims 9-18 are pending in the case.

The new compounds described in this application are useful as 5-HT$_1$ receptor agonists, which exhibit selective vasoconstrictor activity and are useful in the treatment of migraine and associated clinical conditions.

Basis for the new claims disclosing the specific compound of Example 5 and the oxalate, succinate, benzoate and hydrochloride salts is to be found in Examples 5, 17 & 18, and at page 4, line 23, respectively.

Claims 1-6 are amended by indicated bracketing to exclude all subject matter except triazolyl indoles.

The term "pharmaceutically acceptable" is being inserted prior to "salt" to indicate the specific genus of salts contemplated by the invention and supported in page 4, lines 13-15. Basis for the utility in the method of treatment claim is present on page 1, lines 14-20 of the specification. It is submitted that all of the above amendments are adequately supported by applicants' specification.

Examiner states --

> Claim 6 generic to a plurality of disclosed patentably distinct species comprising indolyl piperidines, indolyl pyrrolidines, tetrazolyl benzothiophenes, imidazolyl indoles, triazolyl indoles, tetrazolyl indoles, etc. Applicant is required under 35 USC § 121 to elect a single disclosed species, even though this requirement is traversed.
>
> During a telephone conversation with Polk on June 16, 1992, a provisional election was made with traverse to prosecute the invention of example 6, first compound of p. 101, claims 108, triazolyl indoles. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-8, remaining subject matter are withdrawn from further consideration by the Examiner, 37 CFR § 1.142(b), as being drawn to a non-elected invention. --

Applicants affirm the provisional election with traverse. Applicants point out, however, that Mr. Polk desired to initially select the compound of Example 5, described

on page 100, lines 25-26, for the provisional election being: N,N-dimethyl-2-[5-(1,2-4-triazol-1ylmethyl)-1H-indol-2-yl]ethylamine, and not the first compound of page 101.

Clarification and correction of this error is requested.

The provisional election is being made with traverse on the grounds that the entire class of compounds is considered to be a single unitary invention, and that different heterocyclic substituents, 1,2,3-triazolyl, 1,2,4-triazolyl, imidazolyl and tetrazolyl would all be found in the same heterocyclic prior art and therefore should not present an undue burden to the Examiner for search purposes. Further, Groups I, II, and III all have a common indole nucleus, which would satisfy the criteria of Harnisch. Reconsideration is respectfully requested.

Claims 1-8 are being rejected by the Examiner allegedly as being drawn to an improper Markush group under judicially created doctrine on the grounds of lack of a common nucleus.

Examiner states --

> According, to the CCPA in In re Harnisch, 206 USPQ 300, 305 (1980), lack of a common nucleus or core is one of the criteria present that authorizes the Commissioner of Patents to restrict an application to a single independent and distinct invention. As noted in claim 1 all elements of the formula (1) $A_1$, $A_2$, X, Y, Z, V, W, E and F are variables, therefore no nucleus or core has been found. Further, the scope of the term "heterocyclic group" is so diverse that unlimited variations of the variables are embraced.
>
> Further, the improper Markush group rejection under judicially created doctrine finds antecedent basis in case law. Compare In re Swenson, 56 USPA 180; In re Ruzicka, 66 USPAQ 226 and In re Winnek, 73 USPQ 225.
>
> This rejection can be overcome by deleting the non-elected inventions from the claims. --

The subject matter of Groups I, III, IV and V pertaining to other than triazolyl indoles has been canceled leaving the triazolyl indoles as the remaining subject matter to be prosecuted. Reconsideration is requested.

Claims 1-8 are rejected by the Examiner and the specification is concurrently objected to under 35 USC § 112, first paragraph, allegedly as failing to provide adequate teaching of how to use the compounds.

Examiner states --

> The specification as originally filed lacks description and adequate enabling support for the claimed method, i.e. "A method for the treatment/or prevention of clinical conditions for which a selective agonist of 5-$HT_1$-like receptors is indicated".
>
> On p. 39 of the specification, two *in vitro* binding tests of the claimed compounds to the 5-$HT_1$-like receptors are disclosed:
>
> 1. The $IC_{50}$ of the claimed compounds for 50% *in vitro* displacement of 5-HT in pig caudate was below 1μM.
>
> 2. The $pEL_{5-}$ of the compounds in an *in vitro* against potency assay using rabbit saphenous vein is not less than 5. This evidence is insufficient to support the claimed method of <u>treating</u> or <u>preventing</u> all indications of clinical conditions of a selective agonist of 5-$HT_1$-like receptor. Because, it is known in the art that 5-$HT_1$-like receptors have many different subtype, e.g. 5-$HT_{1a}$, 5-$HT_{1c}$, etc. According to Martin (Arch. Pharmacol. (1449) p. 111, p. 112, left col. 1st paragraph), central 5-$HT_1$-like receptor subtypes are distinct and each subtype correlates to certain potency of function. Therefore, in absence of specific comparison between applicants' compound and known compound, evidence is lacking in the record for potency of function of applicants compounds. The peripheral 5-$HT_1$-like receptors are of ell-defined class and no correlation of this ill-defined class of peripheral 5-$HT_1$-like receptors to its functionality has been discussed.
>
> Survey of the prior art of record, support can be found for only the indolyl compounds of applicants' for treating migraine (see Poenicke and EP 313397). --

Claim 8 has been amended to read on a method of treatment and/or prevention of migraine and associated clinical conditions which are listed on page 1, lines 17-20.

Data to substantiate this is given in applicants' specification on page 39, lines

9-20. Note that positive results are indicated, which is accepted in the art as being evidence for the utility of treatment and prevention of migraine and associated clinical conditions. Note that the rabbit saphenous vein assay used is substantially identical to that described by Robertson in EP Publication 0 313 397, page 39, which Examiner is citing against the instant case as prior art. In summary, the utility is alleged by applicants, data is presented, and evidence of acceptance by the art of that data supporting the utility is also given. Reconsideration respectfully requested.

Claims 1-5 and 8 are being rejected by the Examiner, under 35 USC § 112, second paragraph, allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following terms are considered by the Examiner to be indefinite: "hydrocarbon", "heterocyclic group", "T represents = N.G", "aryl", "heterocycloalkyl, heteroaryl, heteroarylalkyl", "clinical conditions for which a selective agonist of 5-HT$_1$-like receptors is indicated", and "a patient in need of such treatment an effective amount".

The Examiner's Section 112 rejection is deemed to be overcome by the above indicated amendments to claims 1-6 and 8. The terms "hydrocarbon" and "heterocyclic group", as well as the terms "aryl" and "heterocycloalkyl, heteroaryl, heteroarylalkyl" are well known terms of the art, which would be perfectly readily comprehensive to the skilled chemist. A comprehensive discussion of the scope of these terms is present in the extensive passage in the description running from page 4, line 33 to page 6, line 25 to support the amendments.

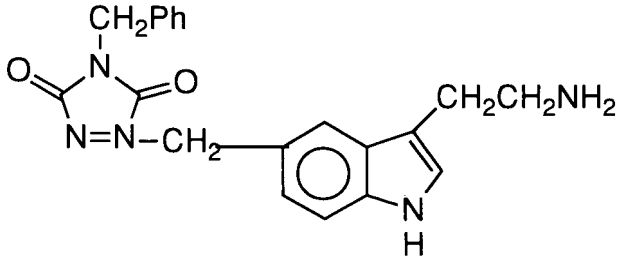
As regards to expression "T represents = N.G", N is the conventional way of referring to a nitrogen atom, and that a definition of the substituent G is provided on page 96, lines 1-2.

In view of the amendment to claim 8, the objections to the expressions "clinical conditions . . . is indicated" and "a patient . . . effective amount" are deemed to be rendered moot, and reconsideration is respectfully requested.

Claims 1-8 are being rejected by the Examiner under 35 USC § 103 allegedly as being unpatentable over Robertson EP 313397.

Examiner states --

Robertson, et al. disclose triazolyl indoles for treating migraines. Compound 24 (of p. 19, line 29) of Robertson are of the structure:



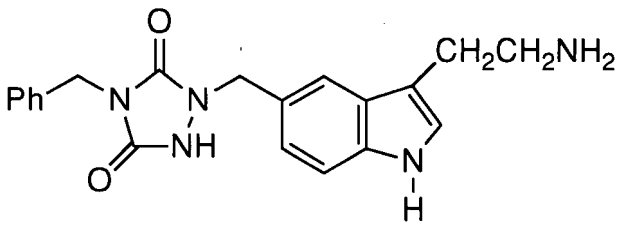

The difference between Robertson's species and the elected invention is that Robertson's compound has dioxo-triazolyl ring while applicants' compounds are triazolyl ring containing.

Generically, Robertson taught the dioxotriazolyl ring and triazolyl ring systems are choices of interchangeable moieties for these compounds (see p. 2 definition of Z and $Z^1$ being C=O or methylene for (iii) or (iv)).

Therefore, applicants' compounds are merely the pick-and-choose among the most compounds generically taught by Robertson. In absence of unexpected results, it is *prima facie* obvious to choose <u>some</u> among <u>many</u>. In re Lemin, 141 USPQ 814. --

The Examiner's position is respectfully traversed.

First of all, it is respectfully submitted that the Examiner has made a fundamental error in drawing the structure of compound 24 of Robertson. There is <u>no double bond</u> in the dioxo-tetrazolyl ring. As drawn by the Examiner, the ring nitrogen atom at the point of attachment to the tryptamine moiety is tetravalent, which would give rise to a quaternary salt, which it is not. The <u>correct</u> structure is as follows:



Thus, the correct structure corresponds to a compound of formula (I) according to claim 1 of Robertson in which the moiety (W) is a group of formula (iii) wherein Y is NH, and Z and Z' are carbonyl groups. The compound as depicted by the Examiner cannot be represented by formula (I) in claim 1 of Robertson.

None of the moieties (i) to (iv) in Robertson contains a double bond within the ring. These moieties are accordingly **heteroaliphatic**. The corresponding moiety in formula I of the instant application, on the other hand, contains **two** double bonds with the ring; this moiety is consequently **heteroaromatic**. The skilled person is well aware that aliphatic and aromatic compounds generally possess markedly differing physical properties. For example, aromatic rings are planar, whereas aliphatic rings generally are not, which means that the rings in question and their attached substituents adopt differing orientations in space. Before the priority date of the present invention, therefore, there was no way in which the skilled person could predict with certainty that the **heteroaromatic** compounds as claimed herein would possess biological activity akin to that alleged for the **heteroaliphatic** compounds disclosed in Robertson, still less from an isolated disclosure of a dioxo-triazolyl derivative. Further, compound 24 is the only compound in Robertson having the dioxo-triazolyl structure; the remaining compounds specifically disclosed by Robertson mainly possess the imidazolidine structure.

The Examiner incorrectly states that "[g]enerically, Robertson taught the . . . triazolyl ring", and this seems to be the source of her confusion. Since, as discussed above, the moieties (i) to (iv) in Robertson lack a double bond within the ring, the relevant moieties should strictly be referred to as triazolidine derivatives, rather than triazole derivatives. Thus, it is simply incorrect for the Examiner to allege that "applicants' compounds are merely the pick-and-choose among the many compounds generically taught by Robertson". A study of the respective disclosures will reveal that there is no overlap between the content of Robertson and any of the claims of the instant application. It follows as a consequence that the present invention cannot be anticipated by Robertson. Further, the applicants believe, for the reasons outlined above, that the instant invention is in no way rendered obvious by Robertson since Robertson does not suggest any heteroaromatic ring, let alone the triazolyl ring. Nor does he suggest their equivalency.

Reconsideration is respectfully requested. Since it is deemed that applicants' claims 1-14 as now amended and argued for, satisfy Sections 101, 112 and 103, allowance of applicants' pending claims is earnestly solicited.

Respectfully submitted,

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